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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,772	02/06/2004	Martin Michaelis	DEA V2003/0008 US NP	7891

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/773,772	MICHAELIS ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-5 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5 and 7 are pending in the application.

Applicant has amended the claims to now read upon treating a degenerative joint disease which includes cartilaginous matrix degradation, in a patient in need thereof, said degenerative joint disease being selected from the group consisting of osteoarthrosis, spondyloses and cartilage atrophy, the method comprising inhibiting cartilaginous matrix degradation.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Claims 1-5 and 7 are presented for examination on the merits as they read upon the elected species, i.e., D-arginyl-L-arginyl-L-prolyl-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-(3R)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-(2S,3aS,7aS)-octahydro-1H-indole-2-carbonyl-L-arginine [i.e.,D-Arg-L-Arg-L-Pro-L-Pro-Gly-Thia-Ser-(3R)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-(2S,3aS,7aS)-octahydro-1H-indole-2-carbonyl-L-Arg]. Please note the following abbreviations and their corresponding equivalents: Thia = 2-thienylalanyl; Tic = 1,2,3,4-tetrahydroisoquinolin-3-yl carbonyl, and Oic = octahydro-1H-indole-2-carbonyl.

REJECTION MAINTAINED

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 7 are rejected under 35 U.S.C. 103(a) as obvious over Nestor et al. (EP 0472 220, cited in the IDS of 02/04) in view of Henke et al. (US 5,648,333, cited in IDS of 02/04).

Nestor et al. (EP 0472 220) teach bradykinin antagonists for treating trauma or a pathological condition induced or mediated by bradykinin, in particular wherein the condition to be treated is a joint degenerative disease such as osteoarthritis (i.e., osteoarthrosis) or rheumatoid arthritis. (e.g., claim 26). The compounds taught by Nestor et al. encompass, within the preferred embodiments, the compound H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-(L)-Ser-(D)-Tic-Oic-Arg-OH (e.g., claims 1-2 wherein A is H, B= D-Arg, C is Gly, Tis Arg, E is Pro, F is Thi (i.e., Thia), G is Ser, I is D-Tic, J is Oic, K is Arg). The limitation of claim 7: "wherein the administration is carried out by

subcutaneous, intraarticular, intraperitoneal or intravenous injection or transdermal administration" is taught, e.g., at page 10, lines 10-58.

Nestor et al. do not teach the specific species H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH, but do teach the species is encompassed by the formula of claim 2 of Nestor et al. A-(B)m-(C)n-T-E-E-C-F-G-I-J-K, wherein A is H, B is Arg, m is 1, n is 0, T is Arg, E is Pro, C is Gly, F is Thi, G is Ser, I is Tic, J is Oic, K is Arg. Claim 26 teaches the use of such compounds for treating osteoarthritis.

Henke et al. teaches the specific compound H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH (see, e.g., Example 60 and column 17, lines 10-18 and 25-67, claims 1, 12, and especially 27-28 and 30) for the treatment of all pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides including arthritis and inflammation (e.g., abstract, column 17, lines 10-17). The limitation of claim 7 is taught, e.g., at column 17, lines 25-67.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of treating osteoarthrosis Nestor et al. by using the specific compound H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH taught by Henke et al. The skilled artisan would have been motivated to do so because Henke et al. and Nestor et al. teach that the compound and family of related compounds treat pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides. There would have been a reasonable expectation of success, given that the species H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH was encompassed within the preferred embodiments of Nestor et

al. to treat degenerative diseases such as osteoarthritis (e.g., claims 2 and 26 of Nestor et al.) and was known to be effective to treat arthritis as taught by Henke et al. Please note that the method taught by Nestor et al. necessarily reads upon the limitation "comprising inhibiting matrix degradation" since the method taught anticipates all the instantly claimed steps of the present invention (i.e., treating osteoarthrosis by administering to the patient a pharmaceutically effective amount of pharmaceutical compositions encompassing claimed compounds). The limitation of claim 7, drawn to different types of administration, is taught, e.g., at column 17, lines 25-67 of Henke et al. and page 10, lines 10-58.

Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

.Applicant's arguments

The primary reference in this rejection is Nestor et al (EP 0472 220). As a preliminary point, Nestor et al. (EP 0472 770) is the equivalent of Nestor et al (AU 638350), which is cited on page 1 of the present specification. For clarity, unless indicated otherwise, all references to "Nestor" will be directed to the above-cited EP document.

In the present action, the Examiner has cited Nestor as teaching that "bradykinin promotes matrix degradation", with reference to page 2, lines 30-36 of the EP document. In the cited passage, Nestor in turn cites a Lerner article from Arthritis and Rheumatism (Lerner), which was cited on page 1 of the present specification in

connection with the citation of the Nestor AU reference. A copy of this article is provided herewith in a separate IDS. Although Nestor mentions "matrix degradation", it is clear from a full reading of the Lerner article that the reference is to bone matrix degradation, not the degradation of the cartilage components of a joint. In particular, line 5 of the abstract of the Lerner article speaks of "bone mineral mobilization and matrix degradation", but later the abstract states "bradykinin .. did not affect the degradation of cartilage proteoglycans.." For this reason, it is stated at page 1, lines 35-37 of the present specification that Lerner teaches that "...bradykinin may actually enhance bone resoprtion, but does not stimulate degradation f the cartilaginous matrix itself". Clearly, there is a distinction between matrix degradation of bone and matrix degradation of the cartilaginous materials in joints.

To emphasize this distinction, present claim 1 has been amended to claim a "method for treating a degenerative joint disease which includes cartilaginous matrix degradation...selected from the group consisting of osteoarthrosis, spondyloses and cartilage atrophy". As such, the Lerner reference, and hence the Nestor reference, clearly teach away from the present invention. There is no teaching in Nestor or Lerner that bradykinin promotes degradation of the cartilaginous matrix of joints, and therefore no teaching that a bradykinin antagonist could be used in the treatment of joint diseases such as osteoatrhorsis, spondyloses and cartilage atrophy. In the present rejection, the secondary reference is Henke et al., which is cited as teaching the compounds fo the present invention and their use for treating "all pathological states which are mediated, caused or supported by bradykinin...". However, as discussed above, the Nestor

reference does not teach that the presently claimed degenerative joint diseases are mediated, caused or supported by bradykinin. Instead, the Lerner article clearly indicates in the detailed discussion at pages 535-536 thereof, that "...the addition of bradykinin... did not affect the release of 35S–sulfate from articular cartilage...". Yet the article goes into great detail on the resorption of bone matrix from selected mouse bones. Therefore, a review of this article shows a distinction in the action of bradykinin on a cartilaginous matrix as compared to a bone matrix. With this reference in mind, it is clear that although Henke teaches that bradykinin inhibition may be useful for treating the painful symptoms of osteoarthritis or rheumatoid arthritis, there is no teaching that bradykinin inhibitors would be useful for treating bone matrix degradation, which is the underlying cause of the degenerative joint diseases to which the present invention is directed.

Response to arguments

Applicants' amendment to include cartilaginous matrix degradation and arguments above have been carefully considered but not deemed fully persuasive for the reasons set forth above and because Lerner et al. (cited in Nestor) teach at page 538, column 1, lines 24-39 that even though PGE2 when applied to culture cartilage alone did not affect ^{35}S-sulfate release, however, when PGE2 was applied together with conditioned medium from synovium cultured in the presence of indomethacin, there was a significant increase in the release of ^{35}S-sulfate. Lerner et al. teach that "Further experiments are planned to investigate the possible role of bradykinin in the interaction

of synovium and articular cartilage". Therefore Lerner et al. (and hence Nestor) do not teach away from teaching inhibiting cartilaginous matrix degradation upon treating osteoarthritis. The 103 rejection is therefore maintained as above.

REJECTION MAINTAINED

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-28 and 30 of U.S. Patent No. 5,648,333 (cited in IDS of 02/04) in view of Nestor et al. (EP 0472 220, cited in the IDS 02/04).

Henke et al. teach the specific compound H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH (claims 1, 12, and especially 27-28 and 30) for the treatment of all pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides including arthritis and inflammation.

Nestor et al. bradykinin antagonists for treating trauma or a pathological condition induced or mediated by bradykinin, in particular wherein the condition to be treated is a joint degenerative disease such as osteoarthritis (i.e., osteoarthrosis) or rheumatoid arthritis. (e.g., claim 26). The compounds taught by Nestor et al. encompass, within the preferred embodiments, the compound H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH (e.g., claims 1-2 wherein A is H, B= D-Arg, C is Gly, Tis Arg, E is Pro, F is Thi (a.k.a. Thia), G is Ser, I is D-Tic, J is Oic, K is Arg).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Henke et al. by treating the specific type of arthritis known as osteoarthritis as taught by Nestor et al. The skilled artisan would have been motivated to do so because Nestor et al. teach preferred compounds comprising the formula H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH to treat bradykinin mediated osteoarthritis. There would have been a reasonable expectation of success, given that both Henke et al. and Nestor et al. teach treating pathological conditions induced or mediated by bradykinin with the same compound. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants' arguments

The cited claims 27-28 and 30 of Henke et al. are directed to compositions and methods for treating a variety of specified conditions including arthritis. There is nothing in these claims about the treatment of degenerative joint diseases such as osteoarthrosis,

spondyloses or cartilage atrophy, and certainly no discussion of treating them by inhibiting cartilaginous matrix degradation. Although a wide variety of pathological states are included in these claims, and although degenerative joint diseases have been known from many years, yet there is no teaching or claim in Henke et al. directed to the treatment of such diseases. The cited claims include a variety of inflammatory diseases, and other diseases which may cause a great deal of pain. However, there is no indication in these claims that the bradykinin inhibitors may be used for the treatment of cartilage matrix degradation associated with degenerative joint diseases. In this rejection, Nestor is cited as a secondary reference to show that such joint diseases are induced or mediated by bradykinin. However, as discussed above, applicants submit that there is no such teaching in Nestor.

Response to arguments

Applicants' arguments have been carefully considered but not deemed persuasive for the reasons of record and the reasons set forth above in response to the previous arguments.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

03/08 MMCG

/Cecilia Tsang/

Supervisory Patent Examiner, Art Unit 1654